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Review

Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis

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SUMMARY

Objective: Emerging evidence suggests that pain sensitization plays an important role in pain associated with knee osteoarthritis (OA). This systematic review and meta-analysis examined the evidence for pain sensitization in people with knee OA and the relationship between pain sensitization and symptom severity.

Methods: A search of electronic databases and reference lists was carried out. All full text observational studies published between 2000 and 2014 with the aim of investigating pain sensitization in humans with knee OA using quantitative sensory testing (QST) measures of hyperalgesia and central hyperexcitability were eligible for inclusion. Meta-analysis of data was carried out using a random effects model, which included results comparing knee OA participants to controls, and results comparing high symptom severity to low symptom severity.

Results: Fifteen studies were identified following screening and quality appraisal. For the meta-analysis, pressure pain threshold (PPT) and heat pain threshold (HPT) means and standard deviations were pooled using random effects models. The point estimate was large for differences in PPTs between knee OA participants and controls [−0.85; confidence interval (CI): −1.1 to −0.6], and moderate for PPT differences between knee OA participants with high symptom severity vs those with low symptom severity (0.51; CI: −0.73 to −0.30). A small point estimate was found for differences in HPTs between knee OA participants and controls (−0.42; CI: −0.87 to 0.02).

Conclusion: Evidence from this systematic review and meta-analysis suggests that pain sensitization is present in people with knee OA and may be associated with knee OA symptom severity.

Introduction

Osteoarthritis (OA) of the knee is traditionally considered a progressive disorder of articular cartilage in the knee joint[1]. Pain presentations associated with knee OA vary considerably and often do not correlate with the severity of joint changes observed radiographically[2]. However, emerging evidence suggests that alterations in nociceptive processing within the peripheral and/or central nervous system may be an important factor in accounting for such variations in clinical presentations of pain associated with knee OA. A number of recent studies have investigated the presence of altered pain processing in knee OA but the precise mechanisms underlying pain sensitization in OA remain elusive[1]. Both peripheral and central neurophysiological mechanisms contribute to the pain of OA. Pain may result from nociceptors of the deep somatic tissue local to the knee becoming sensitized during inflammation (peripheral sensitization) and/or pathological neural signals from the joint causing central nervous system changes (central sensitization)[3]. A greater understanding of, and ability to clinically identify, pain mechanisms in knee OA could be integral to the designation and development of appropriate treatment interventions aimed at optimizing pain relief.

There is currently no gold standard measure with which to assess for and identify the presence of pain sensitization in humans[4]. A number of different measures have been used to assess pain sensitization in people with knee OA. A commonly used method of assessment is quantitative sensory testing (QST), which

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involves the assessment of sensitivity to noxious or innocuous stimuli using standardized mechanical, thermal and/or electrical test modalities[5,6]. Studies have also employed tests of central pain augmentation processes believed to be involved in pain sensitization[1,4,7] such as temporal summation (TS), conditioned pain modulation (CPM) and the flexor withdrawal response (FWR). Methods of assessing these mechanisms are described below. A recent systematic literature review considered evidence for the presence of sensitization in people with OA of the hip, knee, first carpometacarpal joint and lower limb[8], and reported that the majority of the literature suggests that the central nervous system becomes hypersensitized in people with OA pain, while another systematic review presented a meta-analysis of pressure pain threshold (PPT) data in people with OA compared to healthy controls and reported that people with OA had lower PPTs at affected and remote anatomical test sites, suggesting pain sensitization[6]. No study to date has provided a meta-analysis of the evidence for pain sensitization specifically in people with OA of the knee. Therefore, to advance and expand upon the work of previous reviews, the aim of the current study was to conduct a meta-analytic review of the evidence for pain sensitization as measured by QST in people with knee OA specifically – with the secondary aim of meta-analytically investigating the presence of pain sensitization in people with knee OA who have high symptom severity vs those with low symptom severity.

Methods

Search strategy

The study is reported in accordance with the PRISMA guidelines for the reporting of systematic reviews. Systematic searches of the following databases were conducted in June 2014: Pubmed 1950–2014, Web of Science 1970–2014, Medline 1948–2014, EMBASE 1980–2014, CINAHL Plus 1937–2014 and The Cochrane Library. Each database was searched using key word combinations. Three groups of keywords were compiled and combined (Fig. 1). Search terms relating to pain sensitization, features of pain sensitization and knee OA were included for identification of relevant articles. Titles were screened by CF and abstracts of potentially relevant articles were reviewed independently by two researchers (CF and CD). Full text articles of relevant abstracts were retrieved for further review by CF and CD. The two researchers then met to discuss which articles were suitable for inclusion and exclusion. Citations were imported into Endnote ×5.

Inclusion/exclusion criteria

The main aim of potentially relevant studies had to be the investigation of pain sensitization using QST measures of hyperalgesia and central hyperexcitability in adult human participants, diagnosed with knee OA *via* the American College of Rheumatology classification, radiographic evidence or people on a waiting list for total knee replacement (TKR). Papers had to be full text observational studies published in the English language in peer-reviewed academic journals, between 2000 and June 2014. A time limit was implemented in order to identify recent evidence. The exclusion criteria ruled out studies in which QST was not the primary testing method, experimental studies i.e., where an intervention was being evaluated, studies that did not assess measures of pain processing, review papers, and studies that included non-knee OA participants in the analysis. A flow diagram of study selection is detailed in Fig. 2.

Data extraction

Data extraction and analysis was carried out according to QST measures of pain sensitization utilized – only measures relating to pain processing were extracted and analysed. These included QST measures of hyperalgesia i.e., pressure hyperalgesia, thermal hyperalgesia, and hyperalgesia to punctate and electrical stimuli, as well as QST measures of central hyperexcitability i.e., TS, CPM and FWR. For meta-analysis of data, means and standard deviations were sourced from the original papers when available, or by contacting the authors. Data that could not be retrieved was interpreted from graphs using digital ruler software (Pascal Free Ruler Version 1.7b5). Studies were classified by study design (case–control, cross sectional or cohort) for the purpose of quality appraisal.

Quality appraisal

The methodological quality of case–control and cohort studies was assessed by two independent reviewers using the Newcastle Ottawa Quality Assessment Scale (NOS). The NOS is an appraisal tool for assessing the quality of non-randomized studies. The NOS is validated[9] and has been recommended by the Cochrane Non-Randomized Studies Methods Working Group[10]. The scale uses a star rating system to judge quality based on three aspects of the study: selection of groups, comparability, and ascertainment of the outcomes of interest. A maximum of nine stars can be awarded. Studies scoring ≥7/9 are considered good quality; those scoring ≥5/9 are fair quality and studies scoring 0–2/9 are poor quality[11]. For cross-sectional studies, quality appraisal was carried out using the relevant criteria of the NOS checklist for cohort studies, as has previously been reported by Meeus *et al.*[10]. For the purpose of this review, 3/3 was considered a good quality cross sectional study, 2/3 was fair and 1/3 was considered poor quality. Studies scoring less than 40% on methodological appraisal were excluded from the review[8] i.e., studies with <4/9 stars and studies with <2/3 stars.

Data analysis

The analysis was undertaken using Review Manager Software Package RevMan 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Meta-analysis of data comparing knee OA participants to healthy controls was performed. In addition, meta-analysis was carried out on data comparing knee OA participants

Group 1 keywords	Group 2 keywords	MeSH terms
(Central/peripheral/pain) sensitization, hyperalgesia, central hypersensitivity, central hyperexcitability, allodynia, pain processing, pain modulation, pain threshold, pain pathophysiology, somatosensory, neuropathic pain, neuropathic-like pain.	Knee osteoarthritis, knee OA, osteoarthritis of the knee, OA of the knee, knee arthritis, arthritis of the knee, knee arthralgia, arthralgia of the knee, degeneration of the knee	"Central nervous system sensitization", "hyperalgesia" and "knee osteoarthritis"

Fig. 1. Search strategy.

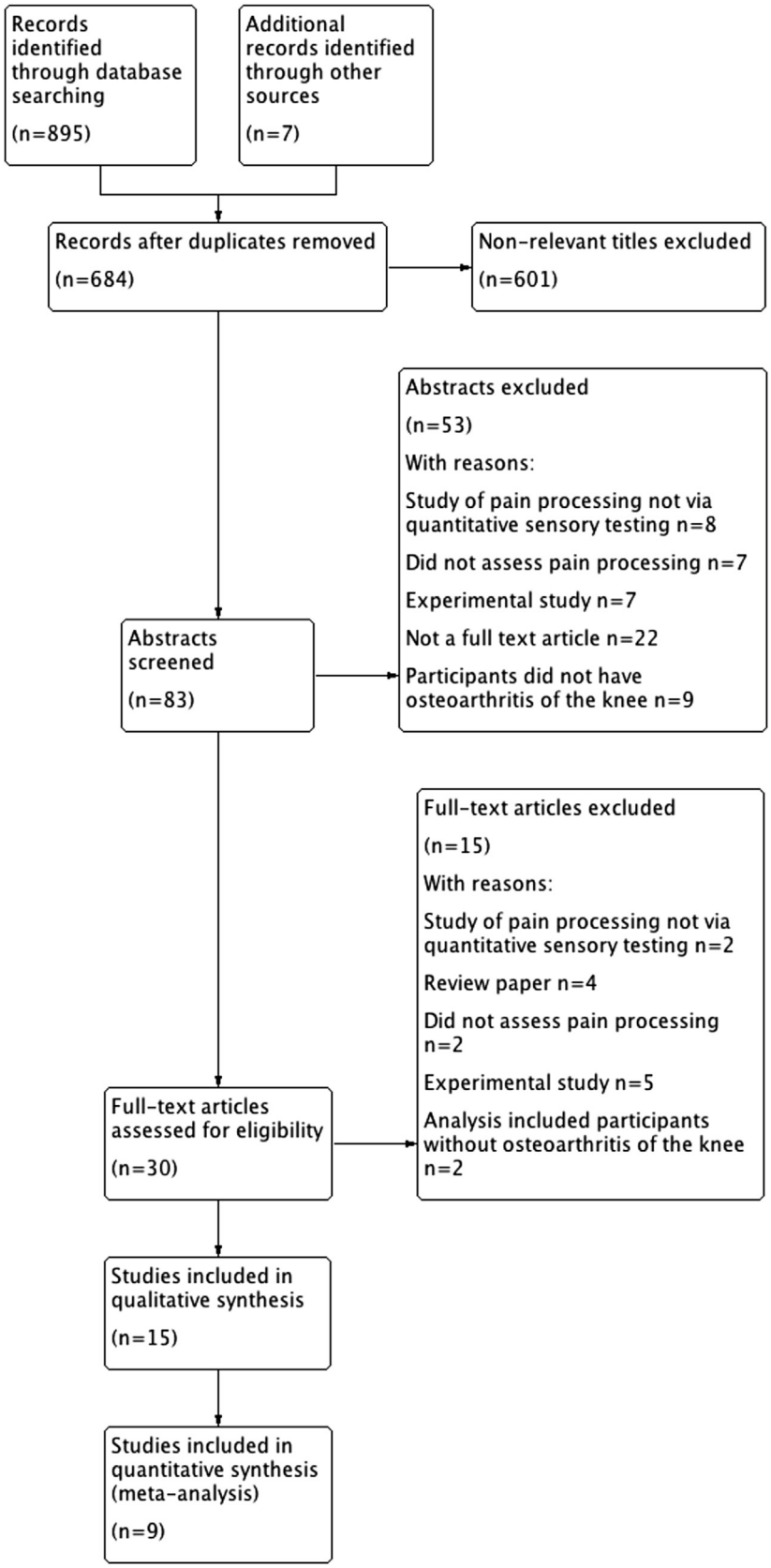

Fig. 2. PRISMA flow chart.

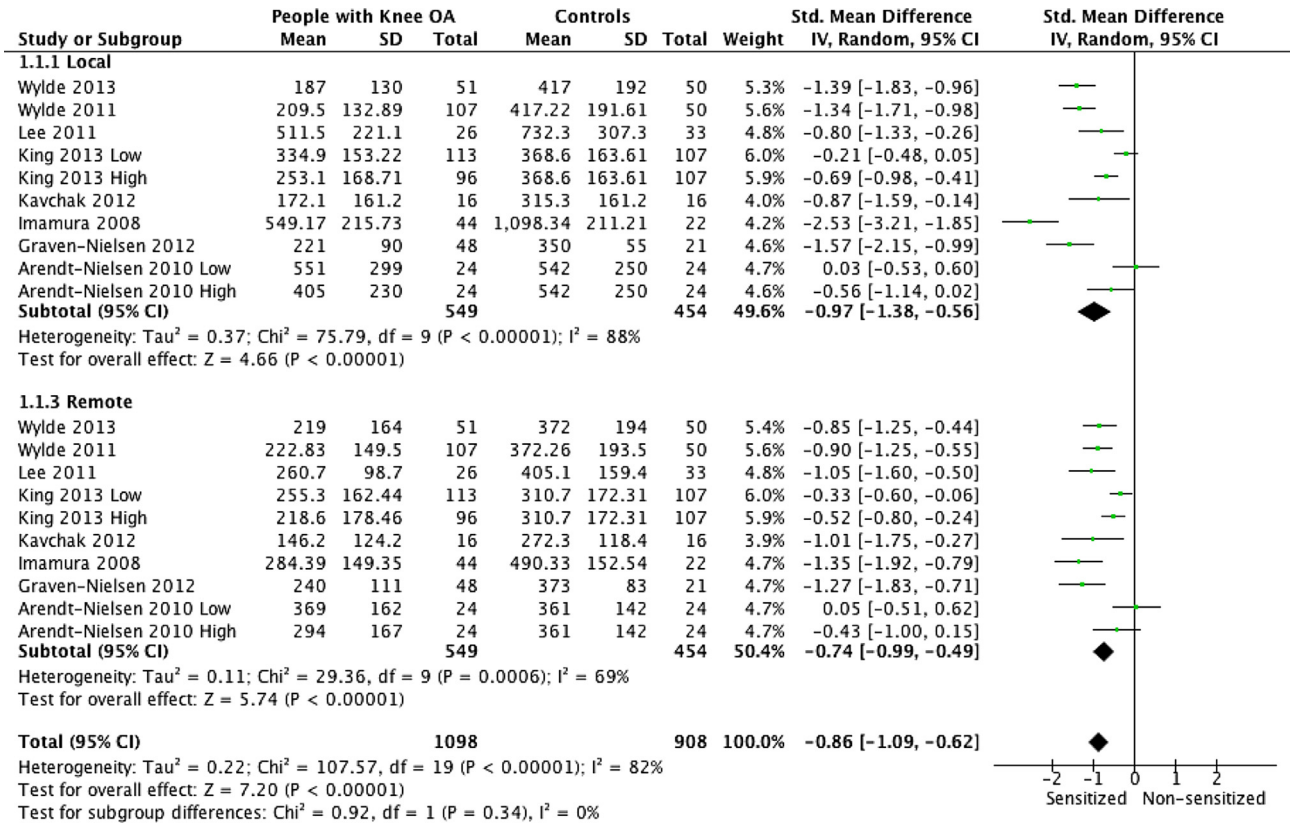

Fig. 3. Results from meta-analysis of PPTs in knee OA participants vs controls. *Note data from Arendt-Nielsen & Graven-Nielsen are interpreted from graphed results.

with high symptom severity to those with low symptom severity. Point estimates on the left side of the forest plots indicated increased features of pain sensitization in knee OA participants and were labelled 'Sensitized', while point estimates on the right side represented the opposite situation and were labelled 'Non-sensitized'. Data which could not be pooled were summarized in narrative format. For continuous data where different scales were utilized for the assessment of the same outcome e.g., PPTs, the standardized mean differences (SMD) with 95% confidence intervals (CIs) were calculated[12]. For continuous data where assessments were made on the same scale e.g., heat pain thresholds (HPTs), the mean differences (MDs) with 95% CI were calculated[12]. Meta-analyses were performed using a random effects model for analyses and pooled point estimate and 95% CIs were calculated with tests of heterogeneity[12]. A funnel plot was conducted for visual inspection of publication bias in the primary meta-analysis (Fig. 6). Point estimates of 0.20 were considered "small", 0.50 was "medium" and 0.80 was considered "large"[13]. The level of significance was set at $P < 0.05$. Measurement areas of hyperalgesia were categorised into (1) local or (2) remote. Local was defined as the over the knee joint or adjacent to the knee joint. When multiple sites around the knee were tested, the site closest to the medial knee was chosen, as this is reported to be the most symptomatic area in people with OA knee[14] and is the area of the knee most

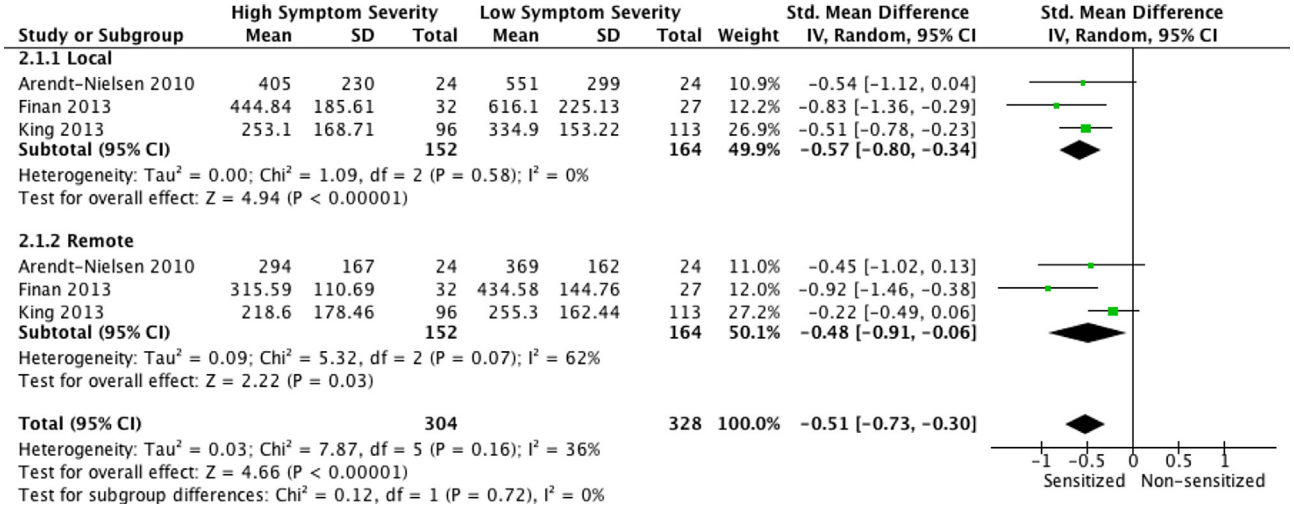

Fig. 4. Results from meta-analysis of PPTs in knee OA participants with high vs low symptom severity. *Note data from Arendt-Nielsen are interpreted from graphed results.

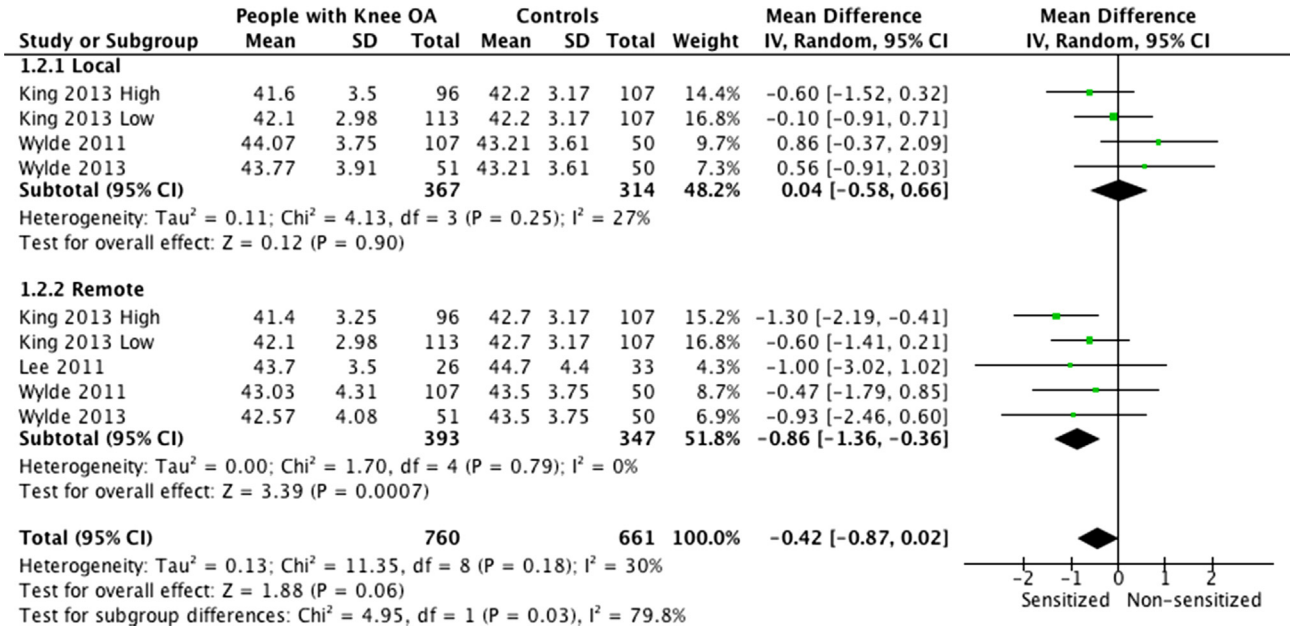

Fig. 5. Results from meta-analysis of HPTs in knee OA participants vs controls.

affected by radiographic change[15]. Remote was defined as a site that was anatomically distant from the primary area of pain. When QST was measured at several remote sites, the furthest site from the knee was chosen (see Figs. 3–5).

Results

Search strategy

The study selection process is presented in Fig. 2. The screening process was carried out by two reviewers. Disagreement between authors was resolved by review of the full paper and further discussion. Fifteen studies were included in the final review (Table I).

Study characteristics

Seven case–control studies[16–22], three cohort studies[23–25] and five cross sectional studies[26–30] were included in the review. Details of study characteristics are outlined in Table I. A flow diagram of study selection is presented in Fig. 2.

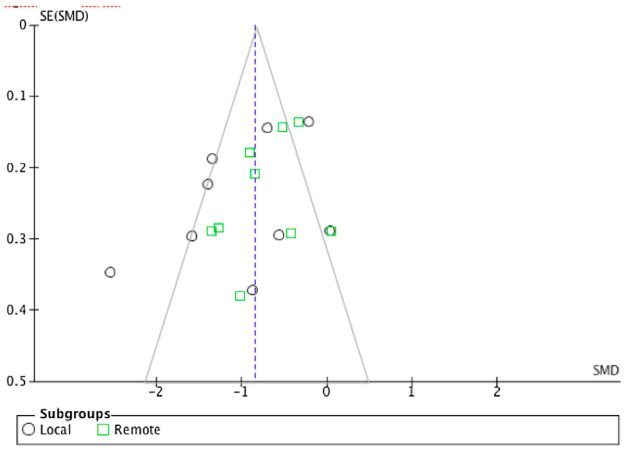

Fig. 6. Funnel plot: PPTs – Knee OA participants vs controls.

Methodological quality

Quality assessment was carried out by two researchers independently. There was an initial 86% agreement between researchers. Any disagreements were resolved by further review of papers until a consensus was reached. Six of the case–control/cohort studies were awarded 5/9 stars (fair quality)[16,18,19,22,23,25], while four case–control/cohort studies were awarded 4/9 stars (poor – fair quality)[17,20,21,24]. Two cross-sectional studies were awarded 3/3 stars (good quality)[26,29] and three were awarded 2/3 stars (fair quality)[27,28,30]. All studies exceeded the 40% threshold for inclusion in the review. Methodological quality was compromised most commonly due to insufficiencies in the representativeness of the knee OA group and appropriate selection of controls (Tables II and III).

Evidence for pain sensitization

Results are presented under headings according to the measures of pain sensitization employed. Meta-analyses of pressure hyperalgesia and heat hyperalgesia are reported below. Results that could not be pooled are summarized in narrative format. Table I outlines the characteristics of included studies.

1 Pressure hyperalgesia

Eleven studies evaluated the presence of hyperalgesia in people with knee OA using measures of PPT[16–19,21–23,25–28]. Eight studies compared PPTs in knee OA participants to healthy controls using handheld pressure algometry and were included in the meta-analysis[16–19,21–23,25]. From a total of 1003 participants: from whom one local and one remote PPT were included (total assessments n = 2006), the point estimate for differences in PPTs between knee OA participants and controls was −0.86 (−1.09 to −0.62), indicating greater pressure pain sensitivity in people with knee OA ($P < 0.001$). A high level of heterogeneity was present ($I^2 = 82\%$, $P < 0.001$). The

Table I
Summary of study characteristics & main findings

Article	Participants	Hyperalgesia measures *(hyperalgesia to pressure, thermal, punctate and electrical stimulation)*	Measures of central hyperexcitability (CPM, TS, FWR)	Results summary
Arendt-nielson, 2010	A. 24 moderate/severe (VAS>6) Knee OA participants (50% female) Mean age: 63.6 Mean pain duration: 95.6 months B. 24 mild/moderate(VAS < 6) knee OA participants (50% female) Mean age: 61.7 Mean pain duration: 78.7 months C. 24 healthy controls (50% female) Mean age: 61.6 Diagnosis: ACR classification	1. PPTs using pressure algometry on eight sites in peripatellar region, TA & extensor carpi radialis longus bilaterally	1. TS of pressure pain using repeated stimuli from computer controlled pressure algometer 2. CPM provocation with cuff compression on arm. PPTs at the knee measured during and 5 min after test.	Group A PPTs were greater than control PPTs, Group A & B TS was higher than control TS. Group A & B CPM was greater than control CPM.
Courtney, 2009	A. 20 knee OA participants Mean age: 61 Mean pain duration: 12.5 yrs B. 20 controls Mean age: 60 (60% female) Diagnosis: ≥2 Kellgren–Lawrence scale	No hyperalgesia measure used	1. Flexor withdrawal response using electrocutaneous stimulation at medial arch of foot	Significantly reduced FWR threshold in OA affected limb vs control group.
Finan, 2012	113 participants with knee OA (66.7% female) Four subgroups: A. low pain/low knee OA grade = 24 B. high pain/high knee OA grade = 32 C. low pain/high knee OA grade = 27 D. high pain/low knee OA grade = 30 Mean pain duration: 6.53 yrs Diagnosis: ACR classification, ≥1 Kellgren–Lawrence scale, pain >2/10 on NRS >4 days/week	1. PPTs (handheld algometry) at upper trapezius bilaterally & quadriceps insertion on index knee	1. TS assessed by repeated punctate stimulation at dorsal aspect middle finger & patella of index knee 2. TS assessed by VAS response to repeated heat pulses (51°) to dorsal forearm 3. CPM provocation by cold pressor test. PPTs measured at trapezius before & after test.	Significantly heightened pain sensitivity in the high pain/low knee OA grade group, while the low pain/high knee OA grade group was less pain-sensitive.
Graven-nielson, 2012	A. 48 knee OA patients (75% female) Mean age: 65 Mean pain duration: 80 months (20 of these underwent TKR) B. 21 age and sex matched controls Mean age: 60 Diagnosis: radiographic	1. PPTs (handheld pressure algometry) at seven sites in peripatellar region, lower leg & forearmbilaterally 2. PPT (Cuff pressure algometry) at lower leg	1. CPM was provoked by cuff compression of arm with ischaemic arm exercise. PPTs at two knee sites & lower leg cuff algometry was carried out during the test	Significantly reduced PPTs in knee, lower leg and forearm muscle in OA participants compared to controls. Dysfunctional CPM present in OA participants Normalization of PPTs and CPM post TKR
Imamura, 2008	A. 62 female knee OA participants Mean age: 71.1 Mean pain duration: 99.8 months B. 22 healthy controls Mean age: 68.95 Diagnosis: ACR classification, 2–4 on Kellgren–Lawrence scale, VAS ≥ 4	1. PPTs with handheld algometry for: Subcutaneous hyperalgesia on dermatome levels L1-S2; Myotomal hyperalgesia on nine Lower limb muscles; Scleratomal hyperalgesia on supraspinal ligaments L1–S2, patellar tendon, pes anserinus bursae bilaterally	No measure of central hyperexcitability used	Significantly reduced PPTs at subcutaneous dermatomes ($P < 0.001$), myotomal structures ($P < 0.001$) & sclerotomal structures compared to controls.
Kavchak, 2012	A. 16 knee OA participants (81.25% female) Mean age: 52 Mean pain duration: 4.09 yrs B. 16 healthy controls Mean age: 51 Diagnosis: by orthopaedic physician, Kellgren-Lawrence scale ≥ 2	1. PPTs using handheld algomety at MJL & lower leg unilaterally	No measure of central hyperexcitability used	Significantly reduced PPTs at MJL in knee OA participants

King, 2013	A. 113 with low symptom severity (73% female) Mean pain duration: 24.7 months B. 96 with high symptom severity (67% female) Mean pain duration: 57.8 months C. 107 healthy controls (66.7% female) Diagnosis: ACR classification, including self reported knee pain	1. PPTs at medial and lateral joint lines of the knee unilaterally, middle portion of quadriceps, forearm, trapezius 2. HPT at forearm using a computer-controlled Medoc Pathway 3. Cutaneous sensitivity at back of hand & patella using monofilaments	1. TS using repeated thermal pulses at forearm 2. TS using repeated punctate stimulation 3. CPM using by cold pressor test. HPTs tested before and after	Significantly reduced PPTs in knee OA participants compared to controls. Significantly reduced PPTs in high symptom severity group compared to low symptom severity group. Greater facilitation of TS in high symptom severity group compared to low symptom severity group No significant difference for HPT between groups.
Lee, 2011	A. 26 knee OA participants (76.9% female) Mean age: 59 Mean pain duration: not reported B. 33 healthy controls (69.7% female) Mean age: 57.7 Diagnosis: documented in medical record	1. PPTs using handheld pressure algometry locally at quadriceps and remotely at trapezius, first metacarpophalangeal joint 2. HPTs with medoc thermal sensory analyzer at ventral forearm 3. Heat pain rating with medoc thermal sensory analyzer at ventral forearm & NRS 4. Cold pain rating with cold pressor test & NRS	No measure of central hyperexcitability used	Significantly reduced PPTs locally & remotely in knee OA group compared to controls. Significantly higher heat pain ratings in knee OA group compared to controls. Non-significant trend for lower HPTs in knee OA group vs controls. No significant difference in cold pain ratings between knee OA group & controls.
Lundblad, 2008	A. 69 knee OA participants for TKR (51% female) Mean age:68 Mean pain duration: 8.5yrs B. 24 controls Mean age not reported Diagnosis: on TKR waiting list	1. Pain threshold with pain matcher (electrical stimulus at finger)	No measure of central hyperexcitability used	Significantly reduced pain threshold remotely at the hand compared to controls.
Neogi, 2013	2126 participants with/at risk of knee OA (61% female) Mean age: 68 Mean pain duration: not reported Diagnosis: radiographic	1. PPTs with handheld algometer at patella bilaterally & at radioulnar joint	1. TS with weighted monofilament	PPT and TS were significantly associated with pain severity. Knee OA duration and radiographic severity were not associated with PPT or TS.
Skou, 2013a	40 people post revision TKR A. 20 with pain (70% female) Mean age: 61.5 Mean pain duration: 167 months B. 20 without pain (40% female) Mean age: 65.7 Mean pain duration: 64.3 months Diagnosis: end stage knee OA patients who underwent TKR & revision TKR	1. PPTs at eight sites in peripatellar area & lower leg with handheld pressure algometry bilaterally 2. PPT using cuff algometry at heads of gastrocnemius	1. TS with computer-controlled pressure algometry at lower leg 2. CPM was provoked by cuff compression of arm. PPT sites assessed before, during & 5 min after	Significantly decreased cuff PPTs at the lower leg in the group with pain post revision TKR compared to the group without pain post revision TKR. Dysfunctional CPM and significantly greater facilitation of TS were present in the group with pain post revision TKR compared to the group without pain post revision TKR.
Skou, 2013b	17 knee OA participants (24% female) 8/17 had undergone TKR Mean age: 65.1 Mean pain duration: 115.1 months Diagnosis: radiological & symptomatic knee OA	1. PPTs at eight sites in peripatellar area & lower leg with handheld pressure algometry unilaterally 2. PPTs using computer-controlled pressure algometry on most sensitive peripatellar site & lower leg 3. PPTs using cuff algometry at heads of gastrocnemius	1. TS with computer-controlled pressure algometry at most sensitive site & lower leg 2. CPM was provoked by cuff compression of arm. PPT sites assessed before, during & 5 min after.	PPTs at the lower leg and TS accounted for 55% of the variance in perceived maximal pain intensity in people with knee OA
Skou, 2013c	73 knee OA/revision TKR participants A. 26 knee OA participants with high local PPTs (38% female) Mean age: 64 Mean pain duration: 86.6 months	1. PPTs at lower leg and forearm using pressure algometry unilaterally	1. TS with computer-controlled pressure algometry at most knee & lower leg	PPTs at lower leg & forearm in Group 4 significantly lower than groups 1–3. TS significantly facilitated in groups 3–4 compared to groups 1–2

(*continued on next page*)

Table I (*continued*)

Article	Participants	Hyperalgesia measures *(hyperalgesia to pressure, thermal, punctate and electrical stimulation)*	Measures of central hyperexcitability (CPM, TS, FWR)	Results summary
	B. 27 knee OA participants with low local PPTs (56% female) Mean age: 61 C. 10 revision TKR participants with high local PPTs (70% female) Mean age: 61 Mean pain duration: 152.2 months D. 10 revision TKR participants with low local PPTs (70% female) Mean age: 61.5 Mean pain duration: 130.9 months Diagnosis: ACR classification			
Wylde *et al*., 2011	A. 107 knee OA participants (48% female) Mean age:69 Mean pain duration: 6 years B. 50 healthy controls Mean age: 68 Diagnosis: on waiting list for TKR	1. PPTs with handheld algometry at forearm & medial knee unilaterally 2. Warm/cold detection & hot/cold PPTs using a QST analyser at forearm & medial knee		Significantly lower median PPTs in knee OA participants compared to controls 32% had local pressure hyperalgesia & 20% had distant pressure hyperalgesia. No significant difference in HPTs between groups
Wylde *et al*., 2013	A. 51 knee OA patients (57% female) Mean age: 68 Mean pain duration: not reported All underwent TKR B. 50 healthy controls (42% female) Mean age: 69 Diagnosis: on waiting list for TKR	1. PPTs with handheld algometry at forearm & medial knee unilaterally 2. HPTs using a QST analyser at forearm & medial knee		Significantly lower PPTs in knee OA group at knee & forearm compared to controls Statistically significant correlation between pre-op forearm PPTs and WOMAC pain 1 year post TKR No significant difference in HPTs between groups & no significant correlation between HPTS and post op WOMAC pain

TS = temporal summation; CPM = conditioned pain modulation; FWR = flexor withdrawal response; ACR = American College of Rheumatology; OA = osteoarthritis; CPM = conditioned pain modulation; PPT = pressure pain threshold; QST = quantitative sensory testing; HPT = heat pain threshold; MJL = medial joint line; TKR = total knee replacement; *Other Non-QST or non-pain processing outcome measures were not included in the analysis.

Table II
Quality appraisal case−control studies

Case− control studies	S1: Adequate case definition	S2: Representativeness of cases	S3: Selection of controls	S4: Definition of controls	Ca: Controlled for age/gender	Cb: Controlled for additional factor	E1: Ascertainment of exposure	E2: Same method for cases & controls	E3: Non-response rate	Total
Arendt-Nielsen, 2010	★			★	★	★	★			5/9 stars
Courtney, 2009	★				★	★	★			4/9 stars
Imamura, 2008	★				★	★	★			4/9 stars
Kavchak, 2012	★			★	★	★	★			5/9 stars
Wylde, 2012	★				★	★	★			4/9 stars
King, 2013	★			★	★	★		★		5/9 stars
Lee, 2011	★			★	★	★	★			5/9 stars

S = selection; C = comparability; E = exposure.

Table III
Quality appraisal cohort/cross-sectional studies

Cohort/Cross sectional studies	S1: Representativeness of exposed cohort	S2: Selection of non-exposed cohort	S3: Ascertainment of exposure	S4: Outcome of interest not present at start	Ca: Study controls for age/gender	Cb: Study controls for additional factor	O1: Ax of outcome	O2: Long enough follow-up	O3: Adequate follow up	Total
Finan, 2012	★		★				★			3/3 stars
Graven-Nielsen, 2012		★	★		★	★	★			5/9 stars
Lundblad 2008			★		★			★	★	4/9 stars
Neogi, 2013	★		★				★			3/3 stars
Skou, 2013a			★				★			2/3 stars
Skou, 2013b			★				★			2/3 stars
Skou, 2013c			★				★			2/3 stars
Wylde, 2013		★	★		★			★	★	5/9 stars

S = selection; C = comparability; O = outcome.
Cohort studies marked out of nine stars, cross-sectional studies marked out of three stars.

funnel plot indicated no significant publication bias (Fig. 6). A meta-analysis comparing Local PPTs between participants with knee OA and controls found that, from 1003 participants, the point difference was −0.97 (−1.38 to −0.56) indicating greater local pressure pain sensitivity in people with knee OA ($P < 0.001$). Again, a high level of heterogeneity was present ($I^2 = 88\%$, $P < 0.001$). Similarly, a meta-analysis of Remote PPTs from 1003 participants demonstrated a point prevalence of −0.74 (−0.99 to −0.49) in favour of greater remote pressure pain sensitivity in the knee OA group ($P < 0.001$). Heterogeneity was high ($I^2 = 69\%$, $P < 0.01$).

Results from three studies comparing knee OA participants with high symptom severity to knee OA participants with low symptom severity[18,19,26] were pooled in a meta-analysis. From a total of 316 participants: from whom one local and one remote PPT were included (total assessments n = 632), the point estimate was −0.51 (−0.73 to −0.30), indicating greater pressure pain sensitivity in the high symptom severity group ($P < 0.001$). Heterogeneity was low ($I^2 = 36\%$, $P = 0.16$). A meta-analysis of Local PPTs in knee OA participants with high vs low symptom severity found that, from 316 participants, the point difference was −0.57 (−0.80 to −0.34), in favour of greater local pressure pain sensitivity in those with high symptom severity ($P < 0.001$). There was no evidence of heterogeneity found ($I^2 = 0\%$, $P < 0.58$). Similarly, a meta-analysis of Remote PPTs from 316 participants demonstrated a point prevalence of −0.48 (−0.91 to −0.06) in favour of greater remote pressure pain sensitivity in the high symptom severity group ($P < 0.05$). Heterogeneity was moderate ($I^2 = 62\%$, $P = 0.07$).

Three additional studies[23,27,29], including one large cross-sectional study of 2,126 people with knee OA[29], found a significant correlation between pressure pain sensitivity and symptom severity. Neogi *et al.*[29] also reported that knee OA duration and radiographic severity were not significantly associated with pressure pain sensitivity ($P > 0.05$). Similarly, Skou *et al.*[27] found no correlation between knee OA pain duration and pressure pain sensitivity ($P = 0.17$).

In relation to studies which measured PPTs pre and post TKR, Graven-Nielsen *et al.*[23] showed that at 5–28 weeks post TKR, pressure pain sensitivity significantly reduced at all sites ($P < 0.04$). However, Skou *et al.*[27] identified increased pressure pain sensitivity in people who had pain post revision-TKR compared to those who were pain-free post revision-TKR. A further study by Skou *et al.* demonstrated that people with high pressure pain sensitivity at the knee post revision-TKR had greater levels of widespread pressure pain sensitivity than people with knee OA (who had not undergone TKR). Wylde *et al.*[25] investigated predictors of persistent pain post TKR and found that people with pressure pain sensitivity at the forearm (remote site) prior to TKR had significantly worse 1 year WOMAC pain scores than people with less pressure pain sensitivity at the forearm preoperatively ($P = 0.031$).

2 Thermal hyperalgesia

The presence of hyperalgesia to hot and cold stimuli has been found in people with chronic musculoskeletal pain[31,32]. The response of participants with knee OA to thermal stimuli was investigated in five studies[16–18,25,26].

Heat hyperalgesia

Four studies comparing HPTs in people with knee OA to healthy controls were pooled in a meta-analysis[16–18,25]. From a total of 740 participants: from whom one local and one remote HPT were included (total assessments n = 1421 – one study measured remote HPT only[16]), the point estimate for differences in HPTs between people with knee OA and the control groups was −0.42 (−0.87 to 0.02), suggesting no significant difference in heat pain sensitivity between knee OA participants and controls ($P = 0.06$). There was a low level of heterogeneity ($I^2 = 30\%$, $P = 0.18$). A meta-analysis comparing Local HPTs between participants with knee OA and controls found that, from a total of 681 participants, the point difference was 0.04 (−0.58 to 0.66), indicating no significant difference between the knee OA group and controls ($P = 0.90$) and a low level of heterogeneity was present ($I^2 = 27\%$, $P = 0.25$). A meta-analysis of Remote HPTs from a total of 740 participants demonstrated a point prevalence of −0.86 (−1.36 to −0.36) indicating significantly greater remote heat pain sensitivity in people with knee OA ($P < 0.001$). There was no evidence for heterogeneity ($I^2 = 0\%$, $P = 0.79$).

With regard to verbal heat pain ratings, Lee *et al.*[16] found that people with knee OA had higher remote heat pain ratings than healthy controls ($P < 0.05$), while King *et al.*[18] found that participants with high symptomatic knee OA reported greater pain upon reaching their HPT at the knee and forearm compared to the control and low symptomatic OA group ($P < .05$), after controlling for the temperature. Similarly, Finan *et al.*[26] found that a knee OA group with high pain intensity/low disease severity had significantly more thermal phasic pain in the forearm than other knee OA groups.

Cold hyperalgesia

It was not possible to perform meta-analysis on the cold pain threshold (CPT) data because of heterogeneity of measures and absence of control data. Overall, no evidence of cold pain sensitivity was evident in the review. King *et al.*[18] found no significant difference in CPTs between knee OA participants and controls ($P > 0.05$). Similarly, Lee *et al.*[16] found no significant difference between knee OA participants and controls for cold pain measured by the cold pressure test, while Finan *et al.*[26] also identified no significant difference between groups of knee OA participants for cold pressor test pain ratings. CPTs were also measured in Wylde *et al.*[17] but were excluded from analysis, as a large number of participants did not perceive cold pain before the safety cut-off temperature of 5°C.

3 Hyperalgesia to punctate & electrical stimulation

King *et al.*[18] demonstrated the presence of hyperalgesia to punctate stimulation in people with knee OA compared to controls ($P < 0.01$). Similarly, Lundblad *et al.*[24] demonstrated that people with knee OA had significantly lower pain thresholds in response to an electrical stimulus delivered remotely at the hand than controls ($P = 0.012$).

4 Temporal summation

Increased TS or wind-up is a measure of spinal hyperexcitability in which the summation of repeated C-fibre input produces an augmented response[33] and is tested by means of repeated noxious stimulation. Four studies demonstrated increased facilitation of TS in knee OA participants[18,19,26,27]. Both Arendt-Nielsen *et al.*[19] and King *et al.*[18] demonstrated greater facilitation of TS at local (knee) and remote (forearm) sites in a knee OA group compared to a non-knee OA group. Arendt-Nielsen *et al.*[19] and King *et al.*[18] demonstrated greater facilitation of TS in participants with knee OA with higher levels of symptom severity than in participants with less symptom severity and controls. Similarly, in the study by Finan *et al.*[26], participants with high pain intensity/low OA severity had a greater TS response at a remote site (finger), than other knee OA participants; however, no significant differences were found between groups in TS measures taken locally at the knee. In a large

cross-sectional study of 2126 knee OA participants, Neogi *et al.*[29] found a significant correlation between TS and pain severity ($P < 0.05$). Neogi *et al.*[29] also found TS was not associated with radiographic changes or knee OA duration; conversely, Arendt-Nielsen *et al.*[19] and Skou *et al.*[27] both demonstrated a statistically significant correlation between TS and knee OA pain duration ($P < 0.05$).

In relation to TS pre and post TKR, Skou *et al.*[28] showed that increased TS was present in participants with pain post revision-TKR compared to participants without pain post revision-TKR when measured remotely at the tibialis anterior (TA) muscle. A further report by Skou *et al.*[30] indicated that TS was facilitated in people with and without high pressure pain sensitivity post revision-TKR compared to people with knee OA (who had not undergone TKR).

5 Flexor withdrawal response

The FWR is a measure of spinal excitability[1] and has been used to demonstrate sensitization in other chronic pain conditions, including chronic whiplash and fibromyalgia[34]. Courtney *et al.*[20] found people with knee OA to have significantly lower FWR threshold than healthy controls ($P = .001$), with specific differences between the more affected limb in the knee OA participants ($P = .0005$).

6 Conditioned pain modulation

CPM is an endogenous pain inhibitory mechanism, which has been found to be impaired in many chronic pain populations[35,36]. Assessment of CPM involves the evaluation of a painful test stimulus in the absence and presence of a second painful (conditioning) stimulus applied to a remote site[37]

Two studies demonstrated a dysfunctional CPM response in people with knee OA[19,23]. Both Arendt-Nielsen *et al.*[19] and Graven-Nielsen *et al.*[24] showed dysfunctional CPM at local (knee) sites in a knee OA group compared to a non-knee OA group; however results differed in relation to remote sites. Graven-Nielsen *et al.*[23] reported CPM dysfunction at the TA, while Arendt-Nielsen *et al.*[19] found a normal CPM response at the TA, but an abnormal response at the forearm – both studies evoked CPM using cuff pressure and used handheld pressure algometry as the test stimulus. Using the cold pressor test as the conditioning stimulus with the test stimulus being handheld pressure algometry, Finan *et al.*[26] found a normal CPM response at the trapezius muscle in four groups of knee OA participants with varying levels of symptom and disease severity. In relation to CPM pre and post TKR, Graven-Nielsen *et al.*[23] found that a CPM stimulus caused a reduction in pressure sensitivity at the knee and a non-significant trend for reduced pressure sensitivity at the lower leg in knee OA participants after TKR. In contrast, Skou *et al.*[27] found that participants who still had pain post revision-TKR demonstrated a dysfunctional CPM response, but a normal CPM response was found in those without pain post revision-TKR. In King *et al.*[18], CPM, provoked by the cold pressor test and tested using HPTs, showed no significant pain inhibiting effect on knee OA or control participants.

Discussion

Findings

Large SMDs in pressure pain sensitivity between people with knee OA and healthy controls is suggestive of nervous system sensitization in this population. This evidence is supported by additional findings of widespread hyperalgesia in response to pressure, punctate and electrical stimuli and by findings from a previous meta-analysis of PPTs[6]. While local findings may indicate peripheral nervous system changes due to prolonged inflammatory processes, findings of hyperalgesia remote to the knee suggest the involvement of the central nervous system. These central changes are thought to be initiated by ongoing pathological neuronal signals from the joint[1,3,4]. Spinal hyperexcitability was demonstrated in knee OA participants in five studies in this review, exhibited *via* increased TS[18,19,26,27] and an exaggerated flexor withdrawal reflex[20]. Results from this review also suggest that endogenous pain inhibitory mechanisms such as CPM are dysfunctional in people with knee OA[19,23]. These findings of sensitization in people with knee OA indicate the potential for additional treatment targets in this cohort where treatment options are generally limited.

Results reported in this review are largely in keeping with sensitization characteristics that have been reported in other chronic pain conditions[10,38]. As such, these conditions appear to share similar pain mechanisms; though, the degree to which this altered processing drives pain appears to vary between conditions and from person to person. While central mechanisms seem to be the driving force behind chronic pain conditions such as chronic whiplash[38] and fibromyalgia[39], it appears to be a subgroup of people with knee OA whose pain is dominated by sensitization. For example, in Finan *et al.*[26], features of pain sensitization were especially apparent in participants with high pain intensity and low disease severity. Additionally, in contrast to findings from other chronic pain populations[31,40], results from the current review suggest that cold hyperalgesia may not be a dominant feature in knee OA pain, with three studies showing no difference in cold pain sensitivity between knee OA participants and controls[16,18,26]. In relation to heat hyperalgesia, the meta-analysis indicated no significant difference in HPTs between people with knee OA and controls. Though, interestingly, when HPTs were sub-grouped into local and remote sites, people with knee OA were found to have significantly greater heat pain sensitivity at remote sites compared to controls, but not at local sites. It is possible that the lack of a significant difference locally between knee OA participants and controls may be linked to the presence of local hypoaesthesia, another sensory abnormality which has been found in people with knee OA[16] and other pain conditions[31,41], and which could potentially influence sensitivity to heat pain. However, such analysis is beyond the scope of this review and warrants further investigation.

The comparison between knee OA participants and healthy controls, while invaluable for determining the presence of altered pain processing in people with knee OA, is limited in terms of deciphering the role that peripheral disease state and pain severity play in pain sensitization. Comparing knee OA participants to each other (e.g., high symptom severity vs low symptom severity; pre-surgery vs post-surgery etc.) provides additional information regarding factors that influence pain sensitization in people with knee OA. A relationship between symptom severity and pain sensitization, as measured by widespread hyperalgesia and TS, is suggested by results from this review. Meta-analysis of data demonstrated significantly greater widespread hyperalgesia in knee OA participants with high symptom severity compared to those with low symptom severity (SMD = −0.51). A cross-sectional study of 2126 people with knee OA supports this relationship, showing symptom severity to be significantly correlated with pressure pain sensitivity and TS. Three additional studies reported greater spinal hyperexcitability, *via* TS, in subjects with high symptom severity vs lower symptom severity[18,19,26]. Furthermore, the large cross-sectional study by Neogi *et al.*[29] reported that pain sensitization was not associated with radiographic severity[29] and Finan *et al.*[26] demonstrated significantly heightened pain sensitivity in a group with high pain severity and low disease severity.

These results indicate a possible link between symptom severity and sensitization, which is independent of radiographic disease severity, and lend support to the concept that peripheral pathology is not the sole driver of painful symptoms in knee OA. However, conflicting results in relation to sensitization and symptom severity have also been reported by studies that used alternative outcome measures. Courtney *et al.*[20] found no significant relationship between FWR threshold, another measure of spinal hyperexcitability, and resting pain. Drivers of spinal hyperexcitability are not fully understood[1]; it is possible that FWR and TS are mediated by slightly different mechanisms. Additionally, Finan *et al.*[26] found no significant difference in CPM levels between four groups of knee OA participants with varying symptom severity; though CPM was within normal limits in all participants in this study. Further investigation is recommended to establish this possible association.

While there is some evidence suggesting that sensitization is linked to pain severity in knee OA, it is yet to be established whether pain sensitivity in this cohort is principally maintained by peripheral pathology. Indeed, the degree of sensitization in knee OA may differ from chronic pain conditions such as fibromyalgia and chronic whiplash due to the presence of an identifiable peripheral pathology in knee OA. Graven-Nielsen *et al.*[23] demonstrated normalization of PPTs and CPM post joint replacement, and normalization of pain sensitivity tests has also been reported post total hip replacement[42]; these findings imply that central changes may be reversible after interventions directed towards peripheral pain generators. However, Skou *et al.*[27] demonstrated pain sensitivity in people with ongoing pain post revision-TKR. The existence of a cohort whose pain is unresolved post repeated surgical intervention suggests that sensitization post surgery may be associated with maintained changes in central pain processing and may be independent of peripheral drivers of pain.

For individuals whose disorder is characterized by sensitization, there is the possibility that central hyperexcitability may be present before knee OA develops, as suggested by Neogi *et al.*[29] in response to findings that duration and radiographic severity of knee OA were not associated with sensitization. The absence of a relationship between disease course and sensitization suggests that there are individuals who may be predisposed to sensitization, and that this trait is uncovered in the presence of nociceptive input from knee OA pathology. Phenotypic and genetic markers associated with chronic pain have been identified[43]. Phenotypic markers such as pain catastrophizing and depression have been found to be significantly associated with QST measures of pain sensitization[26,44], while genetic markers most commonly linked to musculoskeletal pain are those relating to adrenergic and serotonergic pathways[45]. A recent review of genetic studies points to certain genes that contribute to increased pain sensitivity and that are also associated with an increased risk of developing chronic pain conditions[46]. Identification of how these markers contribute to pain perception would enable more specific and personalized therapies for individuals with knee OA in whom sensitization is a primary feature.

Limitations

This review had a number of limitations. Heterogeneity was high for the meta-analysis of PPT data. The source of heterogeneity could not be explained by variations in testing site, as the I^2 value was high in the subgroup analysis also. A random effects model was used to help account for this. Results could not be pooled for all pain sensitization measures, as assessment methods for many of the outcomes were not homogenous. However, results that could not be pooled are summarized and discussed in narrative format and are considered in relation to pooled results. Studies in this review did not rank as high quality on the Newcastle Ottawa Scale. Weakness in study quality was most often related to representation of the knee OA population. Most knee OA participants were sampled from an outpatient hospital population, therefore the extent to which these findings may be generalized to primary care is not known.

Implications for research and clinical practice

Investigation is needed regarding criteria to identify people with knee OA in whom sensitization plays a dominant role. Studies, thus far, have used a wide variety of assessment methods, which is likely to be responsible for some of the variation in results reported in this review. Greater standardization of measures is recommended to allow for replication and verification of findings on this topic. Based on this review, suggested methods for measuring sensitization are PPT measurement at a local and remote site to test for widespread hyperalgesia; CPM using PPT as the test stimulus to assess a descending inhibitory pathway; and TS to assess spinal hyperexcitability. The FWR could also be used where feasible as an objective measure of spinal hyperexcitability alongside TS. It is also recommended that average pain over the past month and radiographic severity be recorded. Assessment of a phenotypic marker such as pain catastrophizing would also be beneficial in terms of recognizing people who may be sensitized. Further investigation into the co-occurrence of thermal hyperalgesia and hypoaesthesia is warranted. In addition, longitudinal research to investigate predictors of ongoing sensitization post TKR is needed. Identifying individuals at risk of persistent sensitization post TKR could allow for targeted pharmacological interventions aimed at reducing sensitization preoperatively. Research is also needed to assess the impact of therapies such as physiotherapy, exercise and psychological interventions on people with knee OA with features of sensitization.

Conclusions

Evidence from this systematic review and meta-analysis of widespread hyperalgesia, spinal hyperexcitability and CPM suggests the presence of a degree of sensitization in people with knee OA. However, the mechanisms by which sensitization may occur in people with knee OA are still unclear. Of note, heat hyperalgesia was shown to be present at remote but not local sites, while there was no evidence for the presence of cold hyperalgesia. In addition, sensitization, as measured *via* pressure pain sensitivity and TS, was shown to be significantly associated with symptom severity, while results suggested no association between sensitization and radiographic severity. Reversibility of sensitization post TKR suggests an association between peripheral pathology and central changes. However, sensitization has also been demonstrated in people post revision TKR, suggesting the presence of a subgroup of people with knee OA whose condition is characterized by central hyperexcitability. The lack of association between disease course and sensitization suggests that the hyperexcitability may, in some cases, pre-exist the knee OA pathology. Future research is needed to identify people with knee OA in whom sensitization is a dominant feature; to establish predictors of ongoing sensitization post TKR and to assess the response of sensitized knee OA groups to commonly used conservative treatments.

Author contributions

Conception and design: CD, CF.
Systematic search: CF.
Study screening: CF, CD.
Quality appraisal: CF, CD.
Interpretation of data: CF, KS, NM, BF, CD.

Meta-analysis of data: CF, BF, CD.
Drafting of the article: CF.
Critical revision of the article for important intellectual content: CD, KS, NM, BF.

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Conflicts of interest
There are no conflicts of interest.

Appendix 1. Search string example

"pain sensitization" OR "pain sensitisation" OR "central sensitization" OR "central sensitisation" OR "peripheral sensitization" OR "peripheral sensitisation" OR hyperalgesia OR "central hypersensitivity" OR "central hyperexcitability" OR allodynia OR "pain processing" OR "pain modulation" OR "pain threshold" OR algometry OR "neuropathic pain" OR "neuropathic-like pain" OR "pain pathophysiology" OR somatosensory OR hyperalgesia [MeSH] OR central nervous system sensitization [MeSH].

AND

"knee osteoarthritis" OR "knee OA" OR "knee arthritis" OR "knee arthralgia" OR "osteoarthritis of the knee" OR "OA of the knee" OR "arthritis of the knee" OR "arthralgia of the knee" OR "degeneration of the knee" OR knee osteoarthritis [MeSH].

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